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The Safety and Effectiveness of Percutaneous Vertebroplasty and Kyphoplasty in Osteoporotic Fractures and Tumors

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Introduction

In the United States, it is estimated that 25% of postmenopausal caucasian women and 35% of women over the age of 65 suffer from osteoporosis, per the WHO definition.(1) Radiographic evidence of osteoporotic vertebral compression fracture (OVCF) exists in 25% of women over 70 and 50% of women over 80.(2) In the U.S., 700,000 of the estimated 1.5 million osteoporotic fractures that occur annually affect the spine.(3) In 1995 there were 120,000 hospital admissions for OVCF and the total cost was reported to be $746 million.(4) By 2030 the projected annual direct costs will exceed $60 billion, or $164 million per day.(4) Similarly, in the E.U. 438,700 osteoporotic vertebral fractures are clinically diagnosed per year (117 per 100,000 person years).(5) The prevalence of OVCFs in Europe is estimated at 1.4 million out of 115 million men and women aged 50-79.(6) In the next 50 years, the incidence of OVCF is likely to increase fourfold.(3)

A major complaint of 85% of patients with a radiological diagnosis of OVCF is back pain, which may be either acute and excruciating or chronic and persistent.(7,8) Acute back pain is usually caused by a recent OVCF, and in the majority of patients is expected to subside as the fracture heals over a period of approximately three months.(9) However, an estimated 33% (10) to 75% (11) of these patients may develop chronic back pain. Chronic pain may arise from persistent intravertebral motion as observed in cases of pseudarthrosis, which can occur with an incidence of 44% per patient or 35% per fracture.(12)

Deformity is another explanation for chronic pain after an OVCF. Furthermore, spinal deformity is a significant cause of disability resulting directly from the impairment of physical functioning, health and quality of life.(13) Kyphotic deformity moves the centre of gravity forward, resulting in increased forward bending moments, which are in turn compensated for by a contraction of the posterior spinal muscles.(13) As a result, the load within the kyphotic angle is increased, predisposing to further vertebral body (VB) fractures.(14-16) Forward bending moment can be counterbalanced by flexing the knees to improve body posture.(17) This posture provokes paraspinal muscle fatigue and increases strain in the facets contributing to chronic back pain. Furthermore, the knee flexion maneuver requires the contraction and tightening of the thigh muscles, resulting in an impaired gait velocity, reduction of mobility and a curtailing of most daily activities, irrespective of pain. The risk of hip fractures increases 4.5 fold after a single OVCF and 7.2 fold after two or more OVCFs, (18,19) independently of bone mass density, (18) possibly reflecting the impaired gait. The impairment of patients' functions leads to sleep disorders, increased anxiety and depression, lowered self-esteem, diminished social role and increased dependency on others.(20-23)

Lung function can be significantly reduced in patients with thoracic fractures. It has been reported that forced vital capacity and forced expiratory volume in one second can be decreased by 9% after each vertebral fracture.(24,25) This may have detrimental effects in patients with preexisting lung disease and result in increased morbidity and mortality. OVCF is associated with a 23-34% age-adjusted increase in mortality rate compared to patients without OVCF.(26,27)

The treatment of OVCF is usually conservative, consisting of analgesics, bed rest and braces. Major reconstructive surgery is indicated for crippling deformities and neurocompression. However, 75% of osteoporotic patients who are treated conservatively may continue to suffer from persistent spinal pain.(28) Therefore, there is room for introducing more effective management of OVCF.

A similar attitude can be used when addressing benign or malignant osteolytic bone tumors (hemangiomas, myelomas, lymphomas and various metastatic tumors) with predictive contribution to bone fragility resulting in VB compression fractures. Radiation therapy gives partial to complete pain relief in 83% to 90% of patients with metastasis to the vertebral bodies,(29,30) usually 10-14 days after the onset of

treatment. Structural strength is minimal and appears after two to four months.(29,30) Furthermore, many osteolytic metastatic lesions often become refractory to chemotherapy and radiation therapy and the patients are moribund to undergo palliative major reconstructive surgery. In these situations, an ideal solution is a minimally invasive technique that addresses both VB stability and pain.

Historical Background – Surgical Technique

The idea of using bone cement to fill bone defects is not new. Bone cement has been successfully applied in filling defects created by giant cell tumors and no failure has been observed during several years of follow-up.(31-34) Polymethyl-methacrylate (PMMA) bone cement was initially used in spinal surgery as an adjunct fixation to spinal instrumentation for the treatment of vertebral compressive fracture caused by osteolytic lesions.(35,36)

Percutaneous Vertebroplasty (PVP) was introduced into the management of osteolytic tumors and later was successfully applied in the treatment of OVCFs. In 1984, Galibert P, a neurosurgeon in St Emien France, invited H. Deramond, an interventional radiologist, to jointly address the problem of a patient with aggressive hemangioma of C2 vertebra causing neurocompression. Deramond successfully injected PMMA bone cement into the lesion,(37) and Galibert proceeded with laminectomy. Subsequently this technique was successfully applied for the treatment of osteolytic metastatic tumors, and multiple myelomas.(38,39) Percutaneous vertebroplasty was introduced in the United States in 1988.(40) The first results obtained with its use in OVCFs were published in 1989.(41) Routine use of the procedure in osteoporosis began in 1995.(42) Since then, several publications have established the usefulness of the technique for osteoporosis.(10,43)

PVP involves injection of PMMA into the treated VB usually through a unilateral or bilateral transpedicular approach or an extrapedicular approach. PVP is usually carried out under local anesthesia and conscious sedation, with constant monitoring of blood pressure (BP), heart rate and pulse oxymetry. The technique is well described in the literature.(42) Gangi et al (44) advocate a combined computed tomography (CT)/fluoroscopic control to guide the transpedicular approach, however, Jensen et al (42) reported that fluoroscopy is easier, safer and less time consuming than the CT.

Percutaneous balloon kyphoplasty (PBK) is a newer technique, which applies the principle of balloon angioplasty to PVP. PBK was primarily invented for the treatment of OVCF, when Mark Reiley, from California had the idea of using an inflatable balloon to restore height in the OVCF in 1993. The void is created after removal of a balloon that is filled with cement.(45-47) PBK is usually performed through the bilateral transpedicular approach for levels between T10 and L5 and the extrapedicular approach above T10 levels. The device was approved as a "bone tamp" by the US Food and Drug Administration (FDA) in 1998.(45) Although initially invented for OVCFs, PBK has been successfully expanded in its indications to include the treatment of osteolytic tumors and myelomas.(47-49) The use of bone cements for vertebral body augmentation by vertebroplasty or kyphoplasty was cleared by FDA in April 2004.(50)

Indications and Contraindications

The indications of cement augmentation are OVCFs, osteolytic tumors, multiple myelomas and hemangiomas. Initially, PVP was limited to patients with OVCFs who did not respond to medical treatment for more than three months.(43, 26) However, because of the low complication rates, as well as the possibility of continued collapse of the fractured vertebra during the period of conservative treatment, early intervention is often advocated.(10) Indications of vertebral augmentation are continuously expanding more liberally to include traumatic fractures,(51-55) treating pain from focal Paget's disease of the spine refractory to medical treatment, (56) painful osteolytic sacral lesion from chylous reflux in patients with lymphangiomatosis (57) and vertebral compression fractures secondary to polyostotic fibrous dysplasia (58) or osteogenesis imperfecta.(59) Open kyphoplasty with direct visualization of the spinal canal has been proposed for vertebral body compression fractures with retropulsed bone producing neurological deficit, in elderly patients who are poor candidate for conventional surgery.(60)

The contraindications for these procedures include: complete loss of vertebral height (vertebra plana), osteoblastic metastatic lesions, burst fractures or high velocity fractures, infections, uncorrected coagulopathy or therapeutic anticoagulation, fractured pedicles, pregnancy, tumors with lysis of the posterior vertebral wall (for vertebroplasty only) and contrast allergy (for PBK – balloons are filled with contrast that can extravasate if ruptured). Although a severely collapsed vertebra is considered as a contraindication, it has been shown that a significant percentage of these vertebrae can re-expand after placing the patient in extension, making the procedure possible.(61,62) For patients under age of 40, cement vertebral augmentation should be used with caution because of the unknown natural history of PMMA in younger patients.

Patient selection

In selecting appropriate patients for PVP and PBK, it is important to distinguish the pain caused by VCF from other causes of back pain. Careful correlation of the patient's history and clinical examination with appropriate imaging documentation of an acute or nonhealed fracture is essential for this purpose.

Clinical assessment: Local tenderness has been emphasized as a cardinal sign of symptomatic fractured ver-

tebra, and has been found to correlate well with magnetic resonance imaging (MRI) or bone scan findings indicating incomplete healing.(63,64) Patients with OVCFs without local tenderness tend to have a long history of back pain, with negative findings from both MRI and bone scan uptake, suggesting healed fractures.(64) Others are of the opinion that pain on palpation over the fractured vertebra is not a necessary requirement in selecting patients who will benefit from the procedure. Gaughen et al (65) reported that in the presence of imaging evidence of unhealed fractures, point pressure tenderness test over the lesion is not necessary for patient evaluation. In a retrospective review of 100 patients treated by PVP they found that in 10 patients with imaging findings suggestive of an acute fracture but negative local tenderness, the results were similar to the rest of 90 patients with positive local tenderness test.

In this group of patients with aging spines, the comorbidity of OVCF with degenerative spinal stenosis should not be of great surprise. In one study this was encountered in 11% of cases necessitating decompressive microforaminotomy.(64) Thus a complete neurological examination is necessary.

Imaging modalities: Anteroposterior and lateral radiographs are essential for identifying radiographic landmarks for planning the trajectory of needle placement. Dynamic lateral radiographs can detect mobile fractures that are prone to re-expansion by extension of the spine. Intravertebral clefts characterizing pseudarthrosis after OVCFs can be easily missed on standing lateral radiographs as they usually became evident on extension and disappear in flexion.(66) In a series of 50 patients (82 VBs), McKiernan et al (12) reported that 37% of VBs contained clefts defined at the time of vertebroplasty as confluent reservoirs for PMMA. Clefts were detectable by standing lateral radiography in only 14% of cases, while 64% of clefts were detectable by supine cross table radiography. Wu et al (67) reported that fractures involving both anterior and middle column have a higher incidence of intravertebal clefts (46.2%) than fractures involving only the anterior column (24.4%).

MRI is the most useful imaging technique for the detection of edema that indicates unhealed fracture and for ruling out malignancy or infection.(68) Sagittal MRI images with short tau inversion recovery (STIR) sequences better highlight the marrow edema that is associated with acute or healing fractures.(69,70) Some investigators have suggested that edema seen on MR images is predictive of a favorable response to PVP.(71-73) Others have questioned its utility, as they reported no direct correlation between symptom resolution and the presence of edema on preprocedural MRI when treating chronic OVCFs with a duration of more than one year.(74) High intensity signal on STIR MRI has also been associated with improved reduction after PBK.(64)

MRI is also more sensitive than plain x-ray films in detecting intravertebral clefts. MRI appearance of intravertebral clefts can vary depending on whether they are gas or fluid filled. The contents of a cleft can vary over time in the supine position, because the gas is progressively replaced by fluid.(66) McKiernan et al (12) reported that 96% of clefts detected during PVP were successfully depicted by the presurgical MRI. On the other hand, Lane et al (75) in a retrospective analysis of 236 OVCFs, reported that only 52.8% of clefts that were noted during PVP were evident on preoperative MRI as fluid filled clefts.

In studies reporting OVCFs older than three months, the incidence of intravertebral clefts is increased. One study using extension radiographs and multiplanar CT scans found that 43% (20/46) of the fractured VBs had clefts.(76) Painful persistent intravertebral mobility explains the good results of cement augmentation in cases of OVCFs older than three months. However, mobility in older OVCFs is not always associated with an intravertebral cleft. In one study, a cleft was detected in only 43% of the OVCFs that showed significant reducibility in extension radiographs.(76) This tends to suggest that part of the mobility is added during hyperlordosis into the trabecular network of the vertebral body.(76)

When patients are unable to tolerate MRI, CT can be helpful. Sagittal reconstructed CT images may be more sensitive than MRI in detecting intravertebral clefts (76) reported that CT examination. CT is also useful in evaluating the integrity of the posterior wall of the vertebral body and to assess posterior displacement of fragments.

A 99Tc-MDP (methyl-diphosphonate) bone scan can provide useful information about remodeling and thereby identify relatively fresh vertebral fractures. However, it may remain negative in cases of vertebral fractures with minimal height loss or remain positive for a prolonged period of time – as long as two years – after fracture has healed, as a reflection of increased remodeling.(77) Furthermore, cases with multiple severe compression fractures, exact labeling of vertebrae on bone scans can be difficult. Although bone scan has a limited ability to demonstrate acute fractures, Maynard et al (78) reported that 93% of patients with multiple fractures of uncertain age, selected by positive bone scan had “marked to complete pain relief.”

Outcomes

Improvement in pain and disability: PVP has been proven highly effective in reducing pain from both OVCF and osteolytic tumors. Existing studies report that an average of 90% (95% CI: 86 to 93%) of patients with OVCF and 86% (95% CI: 76 to 92.5%) of patients with osteolytic tumors experience partial or complete pain relief after the procedure.(79) Change in the Visual Analogue Score (VAS) for pain is reported to range between 4 (52) and 8 (80) degrees in the 10 grade scale. Improved functional levels and reduced need for analgesic medication have also been reported.(42, 81-84) The outcomes of the procedure have been measured using several scoring systems. Zoarski et al (85) reported

improvement in treatment score, pain and disability, physical function, and mental function at two weeks after PVP using the Musculoskeletal Outcomes Data Evaluation and Management Systems (MODEMS) scale. Cortet et al (43) reported improvement in the Nottingham Health Profile scores. Others have reported decreased pain and disability in the Roland-Morris Disability Questionnaire.(86,87) The Oswestry Disability Index has also been utilized by many authors.(87,88)

Similarly, other published reports suggest that PBK can provide excellent pain relief in the majority of patients. An average of 94% (95% CI: 88 to 97%) of patients with OVCF and 93% (95% CI: 75 to 98%) of patients with osteolytic tumors report good to excellent pain response.(79) An overall change in VAS of -5.11 (95% CI: -5.52 to -4.49) has been tabulated in a recent meta-analysis.(89) Ledlie and Renfro, (90) in a retrospective series of 96 patients, reported that the mean pain score in the 10 grade VAS dropped from 8.6 to 2.7 in the early postprocedure period, with a further drop to 1.4 at the one-year follow-up. Activity levels improved dramatically in most patients. There are reports of significant change in the measures for bodily pain and physical function on the Short Form-36 questionnaire (46,91), the Oswestry Disability index (48,64,91-93) and the Ronald Moris Questionnaire.(94)

Restoration of ambulation: Another major benefit of vertebral augmentation is its ability to restore ambulation in 73% of nonambulatory cancer patients (95) and 80% to 100% of severely handicapped osteoporotic patients.(64,90,96-98) Furthermore, even in ambulatory patients cement augmentation has been reported to reduce the days spent in bed and the proportion of subjects reporting no days in bed because of back pain.(93)

Long-term outcomes of cement augmentation for OVCFs: Grados et al (99), in a retrospective analysis of 25 patients treated with PVP, with a mean duration of follow-up of 48 months (range 12-84 months) mentioned that there was no statistical difference between the degree of pain at one month and at the long term follow-up. Similar results were reported by Zoarski et al, (85) who performed a prospective analysis of 30 patients undergoing PVP for OVCFs, with follow-up periods as long as 18 months. The patients were evaluated with the MODEMS scale. Significant improvement was noted in pain and disability levels, physical and mental function by two weeks and continued up to the 18-month follow-up visit. McGraw et al (100) prospectively evaluated 100 patients who underwent PVP for OVCFs (92 patients) and neoplasms (5 patients). In this group, 97% of patients reported significant pain relief at 24 hours that was sustained for a mean follow-up duration of 21 months. The pain scores dropped from 8.9 to 2.0 and 93% of patients noted an increased activity level. Perez-Higueras et al (80) in a prospectively assessed group of 12 patients reported a large decrease in VAS pain scores (9.1 dropped to 2.1) on the third postoperative day that remained steady at the five year follow-up (VAS:2.2). Prather et al (87) reported that the Oswestry low back pain disability score and the Roland-Morris score demonstrated significant functional improvement from baseline to one month after PVP and the improvement remained without significant change at the one year follow-up. These studies conclude that the initial good results seen with cement augmentation can last in the long term follow-up. Similarly, studies in PBK report that pain relief and disability scores improvement were sustained for a mean follow up ranging from 1.5 years (91) to two years.(93,101)

Effect of fracture age: PVP is an efficacious therapy in selected cases regardless of fracture age.(72,73,102) Kauffman et al (72), in a retrospective study of 75 patients with pain duration varying from less than one week to 104 weeks, reported that PVP is a highly efficacious therapy for relief of pain and improvement in mobility, regardless of fracture age. The authors conclude that patient selection for PVP should not based on the age of OVCF but largely on evidence of nonhealing on bone scans or MR images and the degree of persistent pain. Brown et al (102) reported complete or partial relief of pain in 80% (33/41) of patients with fractures who underwent PVP one or more years after the fracture and in 92% (45/49) of patients with fractures less than 1 year old. In this series, patients with chronic fractures tended to have partial rather than complete relief of pain.(102) Alvarez et al (73) reported that within the first year, they did not find any statistical association between fracture age and the outcome after PVP. However, when PVP was performed in patients with symptoms lasting for 12 or more months, “marked to complete pain relief” was only obtained in patients with an abnormal marrow signal on an MRI and a height loss of less than 70%. On the other hand, Brown et al (74) reported that absence of abnormal marrow signal does not definitively predict the outcome of PVP in chronic fractures. In that study, 87% (39/45) of patients with compression fractures older than one year derived clinical benefit from PVP irrespective of MRI findings.

Similar results have been obtained from PBK. Crandall et al (63) reported that 90% of acute (less than 10 weeks) and 87% of chronic (more than four months) fractures were associated with pain relief. Majd et al (103), in a retrospective study in with fracture age at time of treatment ranging between two days to two years, reported that in nonhealed painful fractures with positive MRI or bone scan, the ability to reduce pain was not related to fracture age. Furthermore, the magnitude of height increase was also not related to fracture age. In a resent prospective multicenter study, Garfin et al (93) reported that improvements in pain and disability were independent of fracture age (>60 vs. <60 days). The mean fracture age was 134±318 days in that study.

Effect of number of treated VBs: There is not conclusive evidence about the effect of the number of VBs treated on outcome after cement augmentation for OVCFs. Alvarez

et al (73) in a retrospective study of 278 patients reported that patients who were treated at one or two vertebral levels showed "marked to complete pain relief" in 66-68% while in patients with three vertebral levels treated, this proportion was reduced to 50%. On the other hand, Singh et al (104) reported that PVP performed at a single fracture level and that performed at multiple fracture levels were equally effective in facilitating long-term pain relief, increased activity level and decreased analgesic use in patients with OVCFs.

Effect of cement volume: No correlation has been found between the volume of cement injected and clinical outcomes.(39,105-107)

Effect of presence of intravertebral clefts: Peh et al (108) first reported a series of 18 patients treated with PVP for OVCFs with clefts. The authors reported complete pain relief in 44.4% of patients, partial pain relief in 33.3% of patients and no change in 22.2% of patients. Chen et al (109), in a retrospective series of 27 patients with clefts reported that all patients were satisfied by the procedure, while average VAS decrease from 74/100 preoperative to 34/100 postoperatively. Krauss et al (110) reported that patients with clefts had the same pain reduction as patients without clefts. Ha et al (88) comparing a group of 39 patients with without clefts 12 patients with clefts reported that the mean score of Oswestry Disability Index and VAS after treatment was higher in the group without clefts.

Effect of vertebral height restoration: Failure to restore VB height does not seem to compromise clinical outcomes in the immediate postoperative period after cement augmentation. Grafe et al (111) in a prospective study, reported no significant correlation between change in vertebra height and the change in pain relief (VAS score) and physical function (European Vertebral Osteoporosis Study score). Feltes et al (112), in a retrospective study failed to demonstrate any restoration of VB height after PBK in 13 patients with OVCFs. Nevertheless, all patients in that study experienced profound clinical improvement. Furthermore, partial vertebral height restoration achieved in a PVP series did not result in additional pain relief or improved quality of life beyond cement fixation alone.(113)

On the other hand, there is some evidence that in the long run, reduction of deformity might improve long-term outcomes. Grohs et al, (92) in a prospective nonrandomized study comparing PVP to PBK for OVCFs, reported that although both methods resulted to a distinct decrease of pain at the immediate postoperative period, in long term follow-up the VAS was better for the PBK group. In this study, PBK resulted in significant reduction in the deformity in 54% of patients while PVP did not achieve any correction. Within the PBK group, the reduction of the wedge was associated with a more pronounced decrease in pain in the long-term follow up. Furthermore, Grafe et al (111) reported that after PBK there was a trend towards a positive correlation between the initial height gain and the improvement of the pain score after 12 months, although this correlation failed to reach significance.

Direct comparison of PVP and PBK: Fourney et al (49) in a retrospective nonrandomized study comparing PBK to PVP, reported equivalent results in pain relief and functional improvement that were sustained during the one year follow-up period (**Table 1**). This study was limited only to cancer patients with pathological vertebral fractures. In a prospective nonrandomized study comparing the two methods for OVCFs, Grohs et al (92) reported that both PVP and PBK resulted to a distinct decrease of pain at the immediate postoperative period. However, after PBK, the pain remained at this low level during the two year follow-up and this result was more pronounced in a subgroup with good reduction of the kyphotic wedge. On the other hand, after PVP the decrease of pain was less pronounced between two months and two years postoperatively. The improvement of the disability was significant only during the first year after PBK. The disability for the PVP treated patients was not changed after the procedure.

Direct comparison of cement augmentation and conservative treatment: In a prospective nonrandomized study, Diamond et al (114) compared the outcomes of 55 patients with acute OVCFs who underwent PVP, with those of 24 patients who declined the procedure. Although there was a dramatic improvement in pain and physical function in the

Table 1. Studies that directly compare PVP with PBK

Authors	Study Design	Follow up	Indication	Tx	N:Pts	N:VBs	Patients with good to excellent pain response	VAS reduction	ODI improvement
Grohs 2005 (92)	Prospective	2 years	OVCF	BKP	28	35		-3.9*, -5.4**	23*, 19**
				PVP	23	29		-4.8*, -2.2**	15*, 9**
Fourney 2003 (49)	Retro	1 year	Tumors	BKP	15	32	80%	-5	
				PVP	34	65	86%	-5	

* at hospital discharge
** at the end of follow-up

PVP at 24 hours, there was no difference in pain or physical function between the two groups at six and 12 weeks follow up. However, this study included only acute fractures (one to six weeks) that would have a good possibility of healing in the following months. A more recent prospective non-randomized study of patients with OVCFs of more than 12 months old reported that PBK significantly reduced pain and improved mobility as compared to conservative treatment.(115) Differences in pain scores between the PBK and the conservatively treated patients remained significant throughout the follow-up period of six months.(115) Nakano et al (116), in another comparative study, reported that calcium phosphate PVP resulted in statistically significant difference in improvement rate on VAS at six and 12 months. Preoperative VAS for the PVP treated group was 7.93, and reduced to 0.7 at six months and 0.67 at 12 months. VAS score at diagnosis was 7.47 for the conservatively treated group and reduced to 2.57 at six months and 1.97 at 12 months. Although these differences are statistically significant, the clinical significance of a 1.3 cm difference on the VAS scale at 12 months remains unclear. However, mean duration of period that the patients required analgesic medication was 8.3 days for those treated with PVP versus 62.2 days in the control group, suggesting a much faster pain reduction after PVP.

There are four studies available that directly compare PBK to conventional medical treatment (111,115,117,118), and they are listed in **Table 2**. According to these reports, PBK consistently improved patients' level of pain and physical functioning immediately after the procedure and the results were sustained at 12-months follow-ups as compared to conventional medical care.

Restoration of Vertebral Height and Kyphotic Deformity

Postural correction: In patients with dynamic fracture mobility, spinal extension can at least partially restore vertebral height and kyphosis. Height restoration seen after PVP is the result of cementing the fractured vertebra after postural reduction.(61,76,119-121) Vertebroplasty failed to achieve any significant degree of vertebral kyphosis correction in fractures that did not show reducibility in the

Table 2. Studies that directly compare cement augmentation (PVP or PBK) with conservative therapy.

Authors	Study design	Follow up	Indication	Tx	N:Pts	N:VBs	Patients with good to excellent pain response	Pain reduction VAS or (%)	Physical function
Weisskopf 2003 (117)	Retro	Three months	OVCF + tumors	BKP	22	37		-6.7 (82%)	
				Cons Tx	20	35		-2.2 (42%)	
Komp 2004 (118)	Prospective	Six months	OVCF	BKP	19	NR		-7.4*	ODI Improvement: 24
				Cons Tx	17	NR		-0.8*	ODI reduction: 72*
Kasperk 2005 (115)	Prospective	Six months	OVCF	BKP	40	72		improved**	EVOS: increased
				Cons Tx	20	33		unchanged**	EVOS: unchanged
Grafe 2005 (111)	Prospective	12 months	OCVF	BKP	40		77.5**		No difference**
				Cons Tx	20		55%**		
Diamond 2003 (114)	Prospective	7.1 months	OVCF	PVP	55	71		-53%*, -77%**	29%*, 36%**
				Cons Tx	24			-5%*, -71%**	0%*, 39%**
Nakano 2006 (116)		17 months	OVCF	PVP	30			-7.2**	
				Cons Tx	30			-5.8**	

VAS: visual analogue score, converted to 1-10 scale
ODI: Oswestry disability index
* at hospital discharge
** at the last follow up visit
N: number, Pts: patients, VBs: vertebral bodies, Tx: treatment, Cons: standard conservative medical care
EVOS: European Vertebral Osteoporosis Study Questionnaire

preoperative dynamic x-ray films.(76) The degree of re-expansion has been shown to be closely related with onset duration.(61) However, even in chronic fractures re-expansion is possible especially in cases of progressive vertebral collapse or pseudarthosis. Dynamic fracture mobility has been reported to range between 35% (119), 62% (122) and 68% (76) of fractured VBs. These differences may reflect variations of the average fracture age and the methodology in obtaining dynamic radiographs between studies. Similarly, the percentage of levels that achieved some degree of correction range between 35% (119), 68% (76), 71.5% (123), 85%, (124, 125) and 92%.(121) Prone position with spinal extension have been reported to improve vertebral kyphosis angle by 3.7° (122) to 8.20 (126), anterior wall height by 19%, and mid vertebral height by 16% (122). Jang et al (120), in a series of patients with single fractures with clefts reported that on standing lateral radiographs mean anterior vertebral height improved from 14.8 mm to 21.8mm with extension of the spine. After PVP, mean anterior height was maintained at 19.8mm. Some authors advocate keeping the patients in the supine position with a soft pillow under the fractured vertebra for one to three days prior to PVP to enhance postural reduction.(61)

Some authors mentioned that intravertebral clefts were always present in mobile fractures and absent in immobile fractures.(119) Nevertheless, as mentioned earlier, the absence of intravertebral clefts does not preclude fracture mobility. There are reports that the presence of intravertebral clefts has no impact on dynamic fracture mobility or the degree of height restoration.(122,124) Carlier et al (76) reported that intravertebral clefts were evident in 65% of mobile fractures; however, correction of kyphosis was significantly greater in fractures with clefts, (76) an observation that was also made by others (67,121). Wu et al (67) reported some correction of vertebral kyphosis after PVP in 82% of the fractures with clefts and in 54.5% of the rest of the fractures. Furthermore, fractures with clefts regained more anterior and middle body height, and achieved a greater reduction in the kyphotic angle.

Hiwatashi et al (124) attributed the increase of height seen after PVP to the injection of high viscosity cement under pressure. Although the authors did not use hyperextension to correct the kyphotic deformity, it is possible that prone position alone, even in the absence of hyperextension might have been accounted for part of the reduction. A biomechanical study using a single vertebral fracture model showed that vertebroplasty increased vertebral height by 2.3mm. The reduction was attributed to the procedure itself, as no reduction maneuver was performed to the fractured vertebrae.(127) However, the use of a single vertebra model with no opposing vertebrae above and below is quite different from the clinical situations. Thus, it is uncertain if these findings would translate to the clinical situation.(127)

Balloon inflation: The percentage of levels that achieved some significant degree of correction by PBK range between 54% (92), 58% (128), 70% (46,47,103,129), 84% (130), 90% (101) and 92%.(64) The technique has been associated with variable results in vertebral height restoration and correction of kyphotic deformity. Some of the variation may be influenced by the age of the fracture, the degree of deformity etc. Many authors agree that the more recent the injury, the better the chances for correction of both vertebral height and kyphotic deformity.(63,128,131) Phillips et al (128), in a prospective study of 28 patients with OVCFs, reported that fractures less than three months old showed better correction with PBK. After this initial period, fracture age did not seem to influence the amount of deformity correction achieved with PBK, as long as MRI was consistent with an unhealed fracture.(128) Similarly, Crandall et al (63) reported that osteoporotic fractures treated within the initial 10 weeks are more than five times as likely to be significantly reducible as compared to fractures older than four months. In this study 20% of chronic fractures and 8% of acute fractures failed to show any vertebral height correction.(63) However, 75% of the chronic fractures were at least partially reducible and kyphosis correction was not statistically different between acute and chronic fractures. Majd et al (103) reported that nonhealed painful fractures with positive MRI or bone scan treated within two days to two years from onset, the magnitude of height restoration is not related to fracture age. Other authors (101,122) have also reported no correlation between height restoration and fracture age or agree that meaningful correction can be achieved even in older fractures, when magnetic resonance imaging shows the typical signal changes suggesting incomplete healing.(64,131)

The ability to restore vertebral height can also be influenced by other parameters. Some authors reported that the more caudal the location of the fracture the better the chances to restore vertebral height.(103,131) Others contradict this observation.(101) No correlation has been found between the volume of cement injected, and the degree of correction during PBK.(131)

Some reports fail to exhibit height restoration despite early intervention, within the first three months of onset of the fracture.(112,132) Others failed to reveal any correlation between height restoration of the fractured vertebra and restoration of sagittal alignment of the spine.(122,133) Pradhan et al (133) reported that the majority of kyphosis correction by the PBK is limited to the treated vertebra, possibly caused by the absorption of most of the correction by the adjacent discs. Therefore it might be unrealistic to expect that a one or two-level PBK will significantly improve the overall sagittal alignment. Global sagittal alignment is more likely to be affected by multilevel kyphoplasty. (133)

Postural correction versus balloon inflation: Differences in the methodology of assessing height restoration or kyphosis reduction do not allow for direct comparison between different studies.(134) However, there is evidence that balloon inflation can have an additional beneficial ef-

fect compared to postural reduction alone in the correction of vertebral deformity.(122,135) Voggenreiter et al (122) reported that additionally to the dynamic, position-related reduction of deformity, inflation of the balloon achieved a further 50% decrease of vertebral body kyphotic angle and 20% increase of anterior vertebral body height. However, after deflation and removal of the balloon some loss of fracture reduction can be expected.(122,136) Shindle et al (135) reported that kyphoplasty provided an additional 46.6% restoration of the lost mid vertebral height over the positioning alone. With operative positioning, 51% of VCFs had >10% restoration of the central portion of the vertebral body, whereas 91% of fractures improved at least 10% following balloon kyphoplasty. In that study, balloon kyphoplasty enhanced the height reduction >4.5-fold over the positioning maneuver alone and accounted for over 80% of the ultimate reduction. Boszczyk et al (137) reported that in severe osteoporotic fractures, average correction of the kyphotic angle of was 5% with kyphoplasty, while vertebroplasty failed to achieve correction.

Effects of absorbable cements in maintaining correction: There is some concern that the use of absorbable cements may result in a rebound of kyphotic deformity in the long run. In a clinical study using calcium phosphate some of the vertebral kyphosis correction achieved by PVP was lost at the six month follow-up.(51,116) This gives raise to the hypothesis that absorption of calcium phosphate may result in rebound of kyphotic deformity in the long run. However, calcium phosphate cement used in PVP has been shown to prevent progressive collapse that is often evident after an OVCF.(116)

Complications

Although PVP and PBK are generally accepted as safe procedures, there are numerous reports on complications that the operator should be aware of. General surgical complications such as cardiac, pulmonary and circulatory are less frequent than those encountered in open surgical procedures. However, complications that can be ascribed to the procedure itself, including perioperative rib fractures, transient hypotension during cement injection, transient increase in pain and infections.

Fractures during positioning the patients

Table 3 summarizes the reported incidence of rib & sternal fracture associated with PVP & PBK. Osteoporotic patients are predisposed to fractures and therefore extra care should be taken to carefully roll over them on a well-padded support. Surgeons and OR personnel should avoid leaning over these frail patients.

Fat embolism

Severe systemic reactions during cement augmentation are rare. Kaufmann et al (139) in a series on 78 patients subjected to 142 PVP, reported no change in mean arterial blood pressure or heart rate during or after the procedure. A statistically significant decrease in percentage of oxygen saturation 10 minutes after PMMA injection was reported in that study, but it was very small and was considered clinically irrelevant. However, vertebral body cement augmentation has been associated with reactions such as systemic hypotension, bradycardia, pulmonary hypertension and oxygen desaturation, similar to those described in cemented total joint arthroplasty.(140) Vasconcelos et al (141) reported a case (1/137 patients) of transient hypotensive reaction during PVP that was attributed to fat embolism. Similar hypotensive reactions are expected to resolve spontaneously after some minutes. However, fatal cases of fat embolism have also been reported after PVP for OVCF (142,143), lytic spinal metastasis (144) and pedicle screw augmentation with cement (**Table 4**).(145) Transesophageal echocardiogram in fatal cases revealed significant showering of fat emboli resulting in complete right heart outlet obstruction.(142)

Increased intraosseous pressure during cement insertion is believed to the causative factor for the drop of the arterial pressure. An experimental sheep model vertebroplasty resulted in a two-phase decrease in arterial blood pressure, regardless of the augmentation material. (146) The first very rapid phase starts at two to five seconds and is caused by a reflex activity that increases the pulmonary vascular

Table 3. Rib and sternal fractures during vertebroplasty or kyphoplasty.

Authors	Procedure	Type of fracture	Number of cases	Incidence
Jensen 1997 (42)	PVP	rib	2/29	4.3%
Lieberman 2001 (46)	PBK	rib	1/30	3.3%
McGraw 2002 (100)	PVP	sternum	1/100	1%
Hodler 2003 (106)	PVP	rib	4/152	2.6%
Evans 2003 (97)	PVP	rib	7/245	2.8%
Alvarez 2004 (73)	PVP	rib	5/260	2%
Voormolen 2006 (138)	PVP	rib	1/112	0.9%
Garfin 2006 (93)	PBK	rib	1/155	0.6%

Table 4. Reported cases of fat/bone marrow embolism during vertebroplasty

Authors	Study design	Indication	Clinical consequence	Incidence
Vasonscelos 2002 (141)	retro	OVCF + tumors	transient arterial hypotension	0.7% (1/137 patients)
Weill A 1996 (144)	retro	Tumors	fatal	2.7% (1/37 patients)
Temple J 2002 (145)	case report	OVCF cement pedicle screw augmentation	fatal	one case
Chen 2002 (142)	case report	OVCF	fatal	one case
Syed 2006 (143)	case report		fatal	one case

tone.(147) The second fall begins at 18 ± two seconds, and is a consequence of fat emboli passing through the heart and getting trapped in the lungs. The first echogenic particles on transesophageal echocardiography suggesting fat emboli are visible at six to seven seconds, and the presence of intravascular fat globules and bone marrow cells in the lungs can be confirmed at autopsy.(146) The responsibility of a reflex mechanism to PMMA injection in the first rapid fall in arterial pressure is also supported by Rudigier and Ritter (148) who pressurized the medullary space of the tibia in rabbits. Although they ligated the femoral vein and the surrounded muscles, thus preventing emboli from reaching the general circulation, they observed a decrease in arterial blood pressure within two seconds after the pressure was applied.

Augmentation of more than one vertebral body has a cumulative effect on fat embolism, causing decline in mean arterial blood pressure, decrease in arterial PaO2 and pH, and steady increase in PaCO2.(146)

Leaching of the cement constituents during injection with passage of methylmethacrylate monomer into the blood circulation could also be a potential cause of systemic reactions. However, although methylmethacrylate monomer was constantly found in blood samples taken during hip replacement, no statistical relation was found between the monomer concentration and a hypotensive event.(149) Furthermore, absence of systemic manifestations such as hives, erythema or bronchoconstriction makes an allergic reaction unlikely.

Systematic hypotension, pulmonary hypertension with secondary right ventricle failure and drop in oxygen saturation in cemented total joint arthroplasty is a time-limited phenomenon. Experimental studies found that pulmonary artery pressure may normalize within 24 hours.(150) In healthy patients, the hemodynamic instability can recover within seconds to minutes, even from large embolic loads. However, the surgeon should be aware of these potential cardiovascular complications especially while performing multiple level PVP. Monitoring of the cardiovascular status is recommended, particularly in patients with an impaired pulmonary and cardiovascular system.(151) Placement of a needle as a vent in the contra-lateral pedicle could be used for decompression of the vertebral body during the injection of bone cement.(151)

Based on the recognized systematic effects of PVP, some recommend that the maximum volume of the injected cement should not exceed 30 ml or three levels per session.(91) Two deaths after multilevel PVP have been reported to the FDA.(152) The first of these patients underwent PVP in 11 levels (T8-L3) and the second in eight levels (T8-L3) in the same setting and both patients expired at the end of the procedure. Although there are reports of treating up to five vertebral levels in one session with PVP (85), treating eight or more levels simultaneously is not an accepted practice.

Increase in pain after the procedure

On some occasions, a transient increase in pain has been described within hours or days after PVP.(39,99,144) The reported incidence varies among authors: 1.2% (3/245 patients) (97), 4% (1/25 patients) (99), 6.2% (1/16 patients) (120), 23.4% (4/17 patients).(153) It usually lasts less than 72 hours and may depend on the amount of cement injected.(144) However, there are reports of permanent worsening of pain in 2% of patients after the PVP.(104)

Procedural technical complications

Fracture of the pedicle during PVP has been reported by Kallmes et al (154) in 2.4% (1/41) of patients, by Hodler et al (106) in 0.6% (1/152) of patients, and by Voormolen et al (138) in 0.9% (1/112) of patients. Diamond et al (114) reported fracture of the transverse process in 3.6% (2/55) of patients who underwent PVP. Garfin et al reported three cases (0.9%) of procedural technical complications from faulty tool (Jamshidi needle or filler device) placement during PBK, that resulted in medial wall breach of the pedicle and inadvertent cement placement into the spinal canal or postoperative hematoma in two patients and spinal cord injury when extrapedicular approach was used at a vertebra with fracture pedicle in one patient.(45) These three patients developed serious neurological complications; partial motor loss that responded significantly to surgical decompression in the first two patients and anterior cord syndrome in the third patient.

Because PBK the procedure requires a larger access path through the pedicle, there are some concerns about greater risk for pedicular fractures. Nussbaum et al (152), after reviewing the reported PBK and PVP complications to the FDA postulated that PBK may have an increased risk of pedicle fracture. Among the 20 cases of neurological complications after PBK reported to FDA during 2001-2002, at least five were caused by breakage of the pedicle, causing either the release of cement into the spinal canal or the development of an epidural hematoma at the pedicle fracture site.(152, 155)

Rupture of the balloon has been reported during PBK with an incidence ranging from 2.3% to 20% per treated VB.(46,63,64) However, other than exposure to small volumes of radiocontrast medium, this is not hazardous.(45) In all instances the ruptured tamp was easily withdrawn. This might have resulted from protruding bony spicules piercing the balloon during the procedure. This problem can be avoided by tamping the drilled channel with a bone tamping device in order to break and dispense osseous spicule.(64)

Other complications include hematoma formation, arterial injury and pneumothorax. The incidence of subcutaneous, puncture site hematoma has been reported to range between 1.7% (2/117) (156) to 8.9% (10/112) (138) in patients treated with PVP. This complication has been related with decreased short term patient satisfaction.(138) Bernhard (157) reported left psoas muscle hematoma associated with intense pain at the right thigh that was felt by the patient as the PVP needle was pulled out of the vertebral body. Biafora et al (158) reported a case of injury to a segmental branch of the L4 lumbar artery following PBK at L5 vertebra. The patient presented 10 days after surgery with pulsatile bleeding from the kyphoplasty site and was managed with embolization. Hodler et al (106) reported two cases (1.3% of patients) that developed small asymptomatic pneumothoraces after PVP in the thoracic region. They also reported one patient with clinical symptoms of noninfectious discitis after PMMA leakage into a disk, but they did not perform biopsy to confirm the diagnosis.

Infection

Deramond et al reported a case of spondylodiscitis after vertebroplasty of a metastatic tumor in an immunosuppressed patient.(159) Nine more cases of infections after percutaneous cement augmentation for OVCFs have been reported in the literature (**Table 5**). Kallmes DF et al (154) reported staphylococcus epidermidis infection after PVP in a severely immuno-compromised patient from high dose steroids. Yu et al (160) also reported a case of osteomyelytis in a patient who underwent PVP one week after urinary tract infection that was treated with antibiotics. The infection became evident one month after the vertebroplasty and was managed surgically by combined anterior and posterior approach. Walker et al (161) reported two cases of osteomyelytis after PVP, which also occurred in patients with previous infections. The first patent had a preexisting urinary tract infection with sepsis and had received antibiotic medications for

Table 5. Reported cases of infection after PVP or PBK.

Author	N:Pts	Pro/Re	Agent	Predisposing factors	Management
Kallmes 2002 (154)	1/41 (2.4%)	PVP	Staphylococcus epidermis	high dose steroids	
Yu 2004 (159)	one case	PVP	no organisms identified	UTI	anterior and posterior approach
Walker 2004 (161)	two cases	PVP	Enterobacter species Staphyloccocus	UTI: one patient discitis: one patient	anterior and posterior approach
Schmid 2005 (162)	one case	PVP	no organisms were cultured	liver cirrhosis	percutaneous aspiration of paravertebral abscess
Majd 2005 (103)	1/222 (0.4%)	PBK		renal transplantation	anterior and posterior approach
Vats 2006 (163)	one case	PVP	Straptococcus agalactiae	diabetes	conservative
Alfonso Olmos 2006 (164)	one case	PVP	Serratia marcescens Stenotrophomonas maltophilia Burkholderia cepacia	none	Anterior and posterior approach
Soyuncu 2006 (165)	one case	PVP			Laminectomy and drainage of epidural abscess

UTI: Urinary tract infection

several weeks prior to the PVP. The second patient had a history of discitis and previous open surgery at the level of PVP. In this patient, osteomyelitis became evident eight months after PVP. Schmid et al (162) reported a case of spondylitis of L3-L5 with paravertebral abscess formation after PVP in a patient with alcoholic liver cirrhosis. This patient was managed successfully with percutaneous aspiration of the paravertebral abscess and antibiotic therapy. Majd et al (103) reported an abscess formation at the treated level that developed two months after PBK for compression fracture related to renal osteodystrophy. Cement mantle had been shifted towards the left psoas muscle and the patient had intractable back and left flank pain. He underwent corpectomy and discectomy with anterior plus posterior spinal fusion, but eventually died of cardiovascular failure. Existing data suggests that history of spinal infection at the operative level and any concurrent infection is a contraindication for PVP or PBK. Patients with severe immunosuppression should also be treated with great caution.

Cement leakage

Cement leakage is a frequent occurrence in PVP (**Table 6**). Although it is well tolerated in the majority of cases, it is also the main source of serious complications such as cement embolism or neurological problems. Most authors agree that in the majority of cases the presence of cement leakage is not associated with the final clinical outcome. However, there are reports that leakage into the epidural space (166) or in the disc (73) reduces the pain relief experienced after PVP.

Examining postprocedural CT scans combined with plain radiographs is the most sensitive way to detect cement leakage. Yeom JS et al (167) reported that plain x-ray films revealed only 66% of the leaks that were identified by the CT scan. Ninety three percent of leakage that occurred via the basivertebral veins and 86% of leakage through the segmental veins were either missed or underestimated on lateral radiographs. Only 7% of the leaks into the spinal canal were correctly identified on radiographs. Therefore, cement leakage is more common than may be detected on plain radiographs.

It has been reported that cement extravasation is more frequent when PVP is applied to metastatic osteolytic tumors or myelomas.(39) Vasconcelos et al (141) didn't observe any major differences in the rate of extraosseous PMMA leakage between OVCFs and malignant lesions, although they noted that venous leaks occurred slightly more frequently in cases of metastatic lesions and severely compressed VBs with fractured end plates had an increased incidence of disc space leaks. Similarly, Mousavi et al (105) concluded that in OVCFs leakage occurred mainly in the disc, whereas in metastatic lesions were found in multiple areas.

Intraoseous venography does not accurately depict the distribution of injected cement and has largely been abandoned (172,175,176), except in cases of hypervascular tumors. Heini et al (177) felt that the risk of cement extravasation is diminished if the cement flow is directed medially. He suggested the use of a side-opening cannule to reduce the incidence of this complication. However, experimental data have shown that cement viscosity represents the most important aspect with respect to extravasation risk.(178) Gelfoam embolization has been proposed as a method to reduce cement leakage during PVP.(170)

The risk of cement extravasation into veins and epidural space increases with the volume of cement insertion.(166) Although the amount of cement injected per BV varies in the literature from 2 -11 ml (39,42,177), some authors warn that attempts to inject more than 5 ml of PMMA per VB should be avoided.(179) Epidural leakage during PVP has been reported to occur more frequently when cement is injected above the level of T7.(166)

There is no consensus in the literature about the risk of cement leakage during PVP in patients with intravertebral clefts. Jang et al (120) reported an incidence of 12.5% per VB treated and postulated that spinal extension creates a void within the VB, thereby reducing the risk of leakage. Similarly, Krauss et al (110) reported cement leakage in 18.2% of VBs with clefts versus 46% in regular OVCFs. On the other hand, Peh et al (108) on a series of 18 patients, reported intradiscal cement leakage in 79% and paravertebral leaks in 42% of the treated vertebrae. Similarly, Ha et al (88) reported a higher incidence of cement leakage in fractures with clefts (75% vs 32.6%). Pseudarthrotic cystic cavity, which may be less permeable to injected bone cement, prevents the cement from interdigitating the microstructure of cancellous bone, rendering it more unstable. A case of anterior cement displacement one month after PVP for a T12 OVCF with cleft has been reported.(180) The patient developed severe back pain radiating to the lower abdomen and paraparesis. Removal of the cement and reconstruction of the spine was achieved by combined anterior decompression and posterior instrumentation.

Balloon inflation during PBK creates an intervertebral cavity that allows a more viscous cement to be slowly inserted, thereby decreasing the risk of extravasation (**Table 7**). In addition balloon inflation compacts the trabecular bone, which may seal potential osseous or venous leak pathways. Phillips et al (183) reported significantly lower extravertebral leaks after injecting contrast material into the void created by the inflatable bone tamps as compared to intravertebral injection of contrast before void creation. Studies in cadavers also support the reduced leak rate with kyphoplasty.(184)

Fourney et al (49), treating metastatic lesions with vertebroplasty and kyphoplasty, reported a 9% incidence of leakage in PVP and 0% in PBK. Gaitanis et al, using a routine postoperative CT scan, reported that in OVCF, leakage in the anterior epidural space was 2%, to the paravertebral region through the lateral wall was 4%, and intradiscal leaks were 4%.(64) Majd et al (103) reported that cement leakage did not appear to be related to the level treated, instead more

Table 6: Incidence and location of cement extravasation during percutaneous vertebroplasty

Authors	Study design	VBs	Ind/tion	Total	Epidural	Foraminal	Intradiscal	Para-spinal	Para-vertebral veins
Studies using CT									
Cortet 1999[43]	Prosp	20	OVCF	65%	15%	0	15%	30%	5%
Perez-Higueras 2002[80]	Prosp	27	OVCF	59%	48%	0	7.4%	0	0
Ryu 2002[166]		347	OVCF	NR	26.5%	NR	NR	NR	NR
Nakano 2002[51]		17	OVCF	NR	48%	NR	NR	NR	NR
Yeom 2003[167]	Retro	76	OVCF	63%	38%	0	0	23%	39%
Mousavi 2003[105]	Retro	19	OVCF	NR	10.5%	0	89.4%	31.5%	0
Alvarez 2004[73]	Retro	423	OVCF	72%	52%		16.7%		17%
Legroux-Gerot 2004[168]	Prosp	16	OVCF	87.5%	12,5%	0	31.2%	31.2%	0
Kobayashi 2005[98]	Prosp	250	OVCF	75.6%	63%		38.6%	12.2%	22.2 %
Schmidt 2005[169]	Retro	29	OVCF	81%					
Voormolen 2006[138]	Prosp	168	OVCF	47%	3%		27%	3%	14%
Bhatia 2006[170]	Retro	49	OVCF	22.5%	2%	NR	14.3	2%	NR
Hodler 2003[106]	Retro	363	OVCF+ tumors	72%	6.1%	5.5%	24.2%	52.3%	-
Cotten 1996[39]	Prosp	40	Tumors	72.5%	37.5%	20%	20%	52%	5%
Alvarez 2003[95]	Retro	27	Tumors	44%	37%	0	3.7%	0	0
Mousavi 2003[105]	Retro	14	Tumors	NR	21.4%	0	57.1%	64.2%	0
Bhatia 2006[170]	Retro	12	Tumors	41.7%	16.7%	NR	NR	NR	NR
Barragan-Campos 2006[156]	Retro	304	Tumors		36.4%	4.5%	6.9	24%	1.2%
Studies using X rays									
Cyteval 1999[10]	Prosp	23	OVCF	34.7%	0	8.6%	21.7%	0	4.3%
Jensen 1997[42]	Retro	47	OVCF	25.5%	2%	0	19%	0	4.2%
Wenger 1999[171]	Retro	21	OVCF	47.6%	23.8%	0	4.7%	14.2%	4.7%
Heini 2000[153]	Prosp	45	OVCF	17.7%	4.4%	0	0	11.1%	2.2%
Grados 2000[99]	Retro	34	OVCF	20.6%	0	0	20.6%	0	0
O'Brien 2000[96]		6	OVCF	33.3%	16.6%	0	16.6%	0	0
Gaughen 2002[172]	Retro	84	OVCF	71.4%	20.3%	0	26%	25%	0
Peh 2002[173]	Retro	48	OVCF	43.7%	0	0	35%	8%	0
Vasconcelos 2002[141]	Retro	172	OVCF	27.3%	0	0	9.3%	1.1%	16.8%
Tsou 2002[84]	Retro	17	OVCF	11.7%	NR	NR	NR	NR	NR
Zoarski 2002[85]	Prosp	54	OVCF	NR	1.9%	NR	NR	NR	NR
Jang 2003[120]	Retro	16	OVCF	12.5%	NR	NR	NR	NR	NR
Carlier 2004[76]	Prosp	46	OVCF	37%	13%		20%	2%	
Nakano 2006[116]		30	OVCF	26.7	20%		6.7%		
Gangi 2003[174]	Retro	868	OVCF+ tumors	3.9%	1.7%	0	1.7%	0.1%	0.3%
Vasconcelos 2002[141]	Retro	33	Tumors	21.2%	0	0	6%	0	15.1%
Fourney 2003[49]	Retro	65	Tumors	9.2%	NR	NR	NR	NR	NR

Table 7: Incidence and location of cement extravasation during balloon kyphoplasty

Authors	Study design	Indication	VB	Total	Epidural	Foraminal	Intradiscal	Paraspinal	Intra venous
Phillips 2003[128]	Prosp	OVCF	61	9.8%	0	0	8.1%	3.2%	0
Kasperk 2005[115]	Prosp	OVCF	72	9.7%	NR	NR	NR	NR	NS
Wilhelm 2003[181]	Prosp	OVCF	56	17.8%	5.3%	0	5.3%3	7.1%	0
Rhyne 2004[94]	Retro	OVCF	82	9.8%	0	0	4.8%	4.8%	0
Berlemann 2004[131]	Retro	OVCF	27	33.3%	0	0	11.1%	22.2%	0
Hillmeier 2004[182]	Prosp	OVCF	192	7%	NR	NR	NR	NR	NR
Lane 2004[130]	Prosp	OVCF	32	15.6%	NR	NR	NR	NR	NR
Gaitanis 2005[64]	Prosp	OVCF	49	10%	1.6%	0	3.3%	3.3%	0
Majd 2005[103]	Retro	OVCF	360	10.6%					
Voggenreiter 2005[122]		OVCF	39	23%			12.8%	5.1%	5.1%
Dudeney 2002[47]	Prosp	MM	55	4%	2%	0	0	2%	0
Fourney 2003[49]	Retro	Tumors	32	0%	0	0	0	0	0
Lane 2004[130]	Prosp	MM	38	26.3%	2.6%	0	18.4%	13.1%	0
Gaitanis 2005[64]	Retro	Tumors	12	8.3%	0	0	0	8.3%	0
Lieberman 2001[46]	Prosp	OVCF+ tumors	70	8.6%	1.4%	0	2.8%	4.3%	0
Coumans 2003[91]	Prosp	OVCF+ MM	188	2.7%	0.5%	0	0.5%	1.6%	0
Weisskopf 2003[117]	Retro	OVCF+ tumors	37	13.5%	NR	NR	NR	NR	NR
Ledlie, Renfo 2006[101]	Retro	OVCF + tumors	151	11.3%	2%		6.6%	2.6%	

MM: multiple myeloma

leaks were associated with using extrapedicular approach compared with a transpedicular approach.

Clinical complications of cement leakage

Cement embolism:

This dangerous complication has been correlated with intraoperative evidence of cement migration through the vena cava (156) and postoperative evidence of paravertebral venous cement leakage.(185) Cement emboli usually lodge to the lungs, although cerebral (186) and renal (187) embolisms have also been reported (**Table 8**). Most cases were treated conservatively, with or without anticoagulation, resulting in satisfactory outcomes. However, in a few instances, patients required intensive care management and operative removal of the cement emboli (190), or even open heart surgery.(192,200) Four deaths from pulmonary embolism of bone cement after PVP have been reported in the literature.(194,193,156,201) Paradoxical cerebral artery cement embolization has also been reported after multilevel PVP.(186) In that patient, multiple pulmonary emboli of PMMA precipitated pulmonary hypertension and right-to-left shunting into the venous circulation through a patent foramen ovale. Park et al (200) reported a case of cardiac perforation (right ventricle) by a fish bone-shaped cement emboli that resulted in acute hemopericardium. The cement emboli were removed by open heart surgery. The authors surmise that acrylic cement of very low viscosity injected into the vertebral body drained into the inferior vena cava through the paravertebral venous plexus, where it hardened and drained into the right ventricle. A similar complication has been reported by Kim et al.(199)

There is only one case of non-fatal cement pulmonary embolism after PBK reported by Garfin (45) in a study of 340 patients (incidence 0.3%). Ledlie and Renfo (101) reported one case of pulmonary embolism that occurred two weeks after the procedure. CT scans showed no evidence of PMMA in the lungs.

Neurological complications

Table 8: Published cases of cement embolism

Author	Indication	Type of embolism	No of cases	Incidence	Clinical consequence	Management
Jensen 1997[42]	OVCF	Pulmonary	2	7%	Asymptomatic	
Padovani B 1999[188]	Langerhans' cell histiocytosis	Pulmonary	1	Case report	Dyspnea, haemoptysis	Anticoagulant
Grados 2000[99]	OVCF	Pulmonary	1	4%	Asymptomatic	
Moreland 2001[189]	OVCF	Pulmonary	2	5.7%	Non fatal	
Amar 2001[81]	OVCF	Pulmonary	3	1%	Dyspnea: 1pt Asymtomatic: 2pts	Not described
Tozzi 2002[190]	Osteogenesis imperfecta	Pulmonary	1	Case report	ARDS, renal failure, Rt cardiac failure	Pulmonary embolectomy
Jang 2002[191]	Multiple myeloma	Pulmonary	3	11%	2pts: mild dyspnea 1pt: asymptomatic	Anticoagulant
Scroop 2002[186]	pedicle screw augmentation	Pulmonary & Cerebral	1	Case report	Pulmonary hypertension	No
Hodler 2003[106]	OVCF & Tumors	Pulmonary	10	6.6%	Asymptomatic	No
Gangi A 2003[174]	OVCF + Tumors	Pulmonary	2	0.23%/VBs	Asymptomatic	No
Francois 2003[192]	OVCF	Pulmonary	1	Case report	Mild dyspnea	Open heart surgery
Bernhard 2003[157]	OVCF	Pulmonary	1	Case report	Asymptomatic	No
Yoo 2004[193]	OVCF	Pulmonary	1	Case report	Fatal	Embolectomy
Stricker 2004[194]	OVCF	Pulmonary	1	Case report	Fatal	Advanced cardial life support
Pleser 2004[195]	OVCF	Pulmonary	1	Case report	Asymptomatic	Anticoagulant
Legroux Gerot 2004[168]	OVCF	Pulmonary	1	6.25%	Asymptomatic	
Charvet 2004[196]	OVCF	Pulmonary	1	1 case	Respiratory and cardiac distress	
Choe 2004[185]	Multiple myeloma	Pulmonary	3	4.7%	Asymptomatic	No
Anselmetti 2005[197]	OVCF & Tumors	Pulmonary	2	3.5%	Asymptomatic	
Seo 2005[198]	OVCF	Pulmonary	1	Case report	Asymptomatic	Vena cava cement removed
Kim 2005[199]		Cardiac perforation	1	Case report		
Park 2005[200]	OVCF	Penetration of the right ventricle	1	Case report	Chest pain hemopericardium	Open heart surgery
Monticelli 2005[201]	OVCF	Pulmonary	1	Case report	Fatal	
Baumann 2006[202]	OVCF	Pulmonary	1	Case report	Asymptomatic	Endovascular retrieval
Chung 2006[187]	OVFC	Renal	1	Case report		
MacTaggart 2006[203]	Multiple myeloma	Pulmonary			Asymptomatic	No
Barragan-Campos 2006[156]	Tumors		2	1.7%	Fatal: 1pt Asymptomatic: 1pt	Anticoagulant
Freitag 2006[204]	OVCF	Pulmonary	1	Case report	Hypotension hypocapnia	Anticoagulant
Quesada 2006[205]		Pulmonary	1	Case report	Asymptomatic	
Righini 2006[206]		Pulmonary				
Liliang 2006[207]	OVCF	Pulmonary		Case report	Dyspnoea, chest pain	Oxygenation diuretics

ARDS: Adult respiratory distress syndrom

Cement leakage into the spinal canal is well tolerated in the majority of cases; however, it can lead to serious neurologic complications even complete paraplegia.(179) Leakage through the basivertebral vein leads to a distribution of cement to the epidural plexus. This type of leakage is relatively symmetrica, is located anterior to thecal sac (167) and is not associated with neurologic complications in the majority of cases. Epidural cement leakage through posterior cortical or pedicular defects can be distributed in the anterior and posterior epidural space, resulting in circumferential constriction. A large amount of PMMA cement can extrude into the spinal canal and obliterate large cross-sectional areas of the spinal canal. This type of epidural leakage is more commonly associated with major neurologic complications.(179,208,209) A case of intradural leakage after dural punch that resulted in a myelographic picture in the spinal canal and severe paraparesis has also been reported.(210)

Cement leakage in the foramen is apparently less well tolerated than in the spinal canal. Cotten et al (39) reported that spinal canal leakage was well tolerated in all 15 patients while two out of eight cases of foraminal leakage were associated with radiculopathy. In most cases it causes transient radicular pain responding well to nerve root bocks, oral steroids or nonsteroidal antiinflammatory medication. However, severe radiculopathy that required surgical decompression has also been described.(10,39,169)

Radiculopathy has also been reported in patients without evidence of foraminal or epidural leakage.(80,156) Therefore, radiculopathy can also be a consequence of cement-related irritation, compression and/or ischemia or needle-induced trauma rather than cement leakage.(156)

Although it seems that cement leakage in the paravertebral soft tissue is almost always asymptomatic, Cotten et al (39) reported a case of transient femoral neuropathy related to PMMA leakage into the psoas muscle. Cyteval et al (10) also reported a 5% (1/20 patients) incidence of crural pain with cement leakage in the psoas muscle. The reported cases of neurological complications caused during PVP are shown in **Table 9**.

Most of the cases of neurological complications after PBK are caused by faulty puncture technique, resulting in pedicle disruption and epidural hematoma or cement leakage into the canal.(45,115,182) The reported incidences of neurological complications caused during PBK are shown in **Table 10**.

From the published reports it is apparent that percutaneous balloon kyphoplasty fares better than vertebroplasty in terms of neurological complications. However, according to the reported cases to FDA, PBK is associated with a larger number of neurological complications than that reported in the literature. During 2001-2002, among 24,500 PBK procedures performed in the United States, there is a report of 20 cases of neurological complications that required spinal decompression surgery.(152) Six of these patients sustained permanent injury despite decompression, including one with motor and sensory paralysis below the umbilicus, two with radiculopathy and two with continued leg weakness (one with complete loss of hip flexion and knee extension). In one of the more serious complications, the surgeon had "great difficulty" entering a fractured T6 after which inflation of the balloon "blew out" the vertebral body. When the surgeon attempted to repair the adjacent fracture at T7, no height reduction was achieved and all of the cement reportedly escaped and extended into the area of the aorta, posterior mediastinum and the right pleural lining. The patient continues to have "horrific constant pain and nerve root damage" requiring treatment with "numerous epidural blocks and narcotic analgesics."(152,155)

The data suggest that kyphoplasty may have an increased risk of pedicle fracture that can lead to spinal compression. At least five of the 20 spinal compressions were caused by breakage of the pedicle during insertion of the 8-gauge cannula, causing either the release of cement into the spinal canal or the development of an epidural hematoma at the pedicle fracture site. Only two reports specified that a pedicle fracture was absent on postoperative imaging. Because no explanation is provided for how the remaining 13 spinal compressions developed, these cases also may have been caused by pedicle fracture. In the case of the adjacent T6 and T7 fractures discussed, the more invasive bone tamp and 8-gauge cannula reduced structural integrity and allowed bone cement to extrude.

Subsequent vertebral fractures

The reported rate of new vertebral fractures, especially in the vicinity of the cemented fracture, has raised concern about a possible increase of this risk (Table 11). Grados et al (99) reported that the incidence of fractures in the vicinity of a cemented vertebra was slightly but significantly increased (odds ratio 2:27), in comparison with the incidence in the vicinity of an uncemented fractured vertebrae (odds ratio 1.44). Similar results have been reported by Legroux-Gerot et al (168) The odds ratio for a vertebral fracture in the vicinity of a cemented vertebra was 3.18 compared with 2.14 for a vertebral fracture in the vicinity of an uncemented vertebral fracture. Most reports agree that about 41% to 67% of the subsequent fractures after PVP occur at the vertebrae adjacent to the previously treated ones (**Table 11**). Similarly, Prather et al (87) reported that 64% of the subsequent fractures were within one or two vertebral levels cephalad or caudal to the previously cemented fracture. New fractures developed in all patients that had received glucocorticosteroids for various medical conditions prior to or at the time of the PVP.

There is increasing evidence that subsequent fractures after cement augmentation tend to occur early in the follow-up period. Uppin et al (218) report that 67% (24/36) of the new vertebral fractures occurred within 30 days after PVP. However, this study reported information only on patients who returned for additional PVP. As a consequence,

Table 9: Reported cases of neurological complications after PVP

Author	Indication	Incidence	Management & Outcome
Paraplegia or paraparesis			
Wenger 1999[171]	OVCF	7,6% (1/13pt)	Decompression Failed to improve
Harrington 2001[208]	OVCF	Case report	Resolved
Ratliff 2001[211]	Tumors	Case report	T1corpectomy Recovered
Moreland 2001[189]	OVCF	5.2% (2/35 pt)	Decompression
Lee 2002[179]	OVCF	12,5% (1/8 pts)	Decompression Died during surgery
Mousavi 2003[105]	OVCF + tumors	4.7% (1/21 pt)	Decompression Recovered
Shapiro 2003[212]	OVCF	Case report	Decompression Improved
Chow 2004[213]	Tumors	6.6% (1/15 pts)	Decompression
Alvarez 2004[73]	OVCF	0.4% (1/260 pts)	Decompression Recovered
Schmidt 2005[169]	OVCF	5% (1/21 pts)	Decompression Improved
Teng 2006[209]		Report of 3 cases	Decompression: 2 pts Conservative: 1 pt
Wu ESJ 2006[214]	OVCF	Case report	Decompression Improved
Radiculopathy			
Cotten 1996[39]	Tumors	10,3% (3/29 pts) Radiculopathy: 2pts femoral neuropathy:1pt	Decompression Recovered Resolved
Weill 1996[144]	Tumors	8.1% (3/37 pts)	Decompression: 2pts Improved: 1 Resolved: 2 pts
Deramond 1998[159]	OVCF + tumors	4% (11/274 pts)	
Wenger 1999[171]	OVCF	23% (3/13 pts)	Resolved
Cyteval 1999[10]	OVCF	5% (1/20 pts)	Decompression Failed to improve
Grados 2000[99]	OVCF	8% (2/25 pts)	Resolved
Barr 2000[215]	OVCF	2,6% (1/38 pts)	Steroids –Resolved
Amar 2001[81]	OVCF	1% (1/97 pts)	Resolved
McGraw 2002[100]	OVCF	1% (1/100 pts)	Resolved
Nakano 2002[51]	OVCF	6.25% (1/16 pts)	Resolved
Lee 2002[179]	OVCF	12,5%	Resolved
Perez-Higueras 2002[80]	OVCF	15.3% (2/13 pt) cement leakage: 1pt no leakage: 1 pt	Steroids –Resolved
Evans 2003[97]	OVCF	0,8% (2/245 pts)	Resolved: 1 pt Improved: 1 pt
Alvarez 2003[95]	Tumors	5% (1/21 pts)	Resolved
Gangi 2003[174]	OVCF + tumors	0,35% (3/868 VBs)	
Hodler 2003[106]	OVCF + tumors	(1/152)	Steroids –Resolved
Vasconcelos 2002[141]	OVCF + tumors	0.7% (1/137 pts)	Resolved
Winking 2004[216]	OVCF	2.6% (1/38 pts)	Resolved
Alvarez 2004[73]	OVCF	4.6% (12/260 pts)	Steroids -Resolved
Cohen 2004[217]	OVCF + tumors	3.4% (5/148 pts)	Nerve root block Resolved
Schmidt 2005[169]	OVCF	5% (1/21 pts)	Decompression Recovered
Barragan-Campos 2006[156]	Tumors	3.4% (4/117 pts) 2 pts:foaminal leakage 2 patients: no leakage	Nerve root blocks Resolved

Table 10. Reported cases of neurological complication after kyphoplasty.

Author	Indication	Incidence	Management & Outcome
Garfin 2001 (45)	OVCF + Tumors	0.9% (3/340 patients) one patient: epidural hematoma one patient: epidural leakage one patient spinal cord injury	one patient: recovered after surgical evacuation one patient: significant recovery after decompression one patient atnerior cord syndrome
Kasperk 2005 (115)	OVCF	5% (2/40 patients) one patient: cord penetration one patient: epidural hematoma	one patient: permanent monoparesis one patient: resolved
Wilhelm 2003 (181)	OVCF	2.9% (1/34 patients)	resolved
Hillmeier 2004 (182)	OVCF	1% (1/102) epidural bleeding	resolved
Majd 2005 (103)	OVCF	(1/222 patients) foraminal leakage	nerve root block resolved
Grafe 2005 (111)	OVCF	one patient: epidural hematoma	

it is possible that patients who sustained subsequent fractures but did not seek intervention were not included. Trout et al (223) reported that the relative risk of adjacent level fracture was 4.62 times greater than that for nonadjacent fracture. Median time until diagnosis of an adjacent fracture was smaller (55 days) that that of nonadjacent fracture (127 days) and that time was also associated with the distance of the nonadjacent fracture. Voormolen et al (138) reported that most subsequent VCFs (16/26) occurred within three months of PVP. Half of the fractures that occurred during the first three months were symptomatic and most of them (68.7%) occurred at adjacent levels. Fractures that occurred between 3 and 12 months after the PVP were less symptomatic and located at levels distant from the initially treated vertebra. In that study, the presence of more than two preexisting VCFs was the only independent risk factor for the development of a new VCF.(138) Similar findings have been reported Tanigawa et al (224), who observed that 43% of incident fractures occurred within 30 days of PVP.

Concerns about the role of intradiscal cement leakage in increasing the risk of adjacent fractures have been raised after a report that in 71.4% of patients, the new fractures were associated with cement leakage into the disc.(219) In that study, VBs adjacent to a disc with cement leakage had a 58% chance of developing a new fracture, compared with 12% of vertebral bodies adjacent to a disc without cement leakage. Furthermore, the average time between PVP and new fracture was 48 days in patients who had cement leakage into the disk and 98 days in patients who did not.(219) However, more recent studies with larger number of patients failed to reveal any significant relation between cement extravasation into the disc and the occurrence of a new fracture.(138,222,225) Voormolen et al (138) reported that although cement leakage to adjacent disc occurred in 30% of treated vertebra, only one of the 14 (7%) new fractures that occurred adjacent to the treated VB occurred in relation to cement leakage to the adjacent disc space.

Subsequent vertebral fractures after PBK: Harrop et al (227) in a retrospective study of 115 patients, reported that the incidence of subsequent fractures after PBK in the primary osteoporotic patients was 11.25% (9/80 patients), while in the steroid-induced osteoporotic patients was 48.6% (17/35 pts). Majd et al (103) reported that 12% of the patients presented with subsequent fractures. However, only symptomatic new fractures that were subjected to additional PBK are reported in this study. Similarly, Ledlie and Renfo (101) reported that during the two-year follow-up, 9% of patients had new symptomatic fractures and underwent an additional PBK. Sixty seven percent of those fractures were adjacent to the treated index VB.

Fribourg et al (226) in a retrospective study of 38 patients with eight months follow-up, reported that 76% (13/17) of the new fractures occurred at adjacent VB (nine above and four below). Patients with subsequent fractures within 60 days after PBK had at least one adjacent level fracture, while patients with late subsequent fractures had remote level fractures. This study revealed a high incidence of subsequent fractures in the first 60 days after PBK, indicating that subsequent fractures are much less likely to occur after this initial period of time has elapsed.

Garfin et al (93) reported that during a two-year follow-up period, 23% of the patients treated with PBK had at least one subsequent painful vertebral fracture. The cumulative probability was 20% at one year and 23% at two years, implying that most of the fractures tend to occur early after treatment. In 61% of these subjects the subsequent fracture was adjacent to a PBK treated VB. Lavelle et al (228) reported that 11 kyphoplasty procedures (10%) resulted in a subsequent fracture within the first 90 days (34±19 days). After the first 90 days, five more subsequent fractures occurred (459±101 days). Patients who sustained a subsequent

Table 11: Incidence of new vertebral body fractures after PVP and PBK for OVCF

Author	Study design	Mean FU	New fractures			
			N:PTs	%:Pts	Fx/TxVBs	Adjacent (%)
PVP						
Jensen 1997[42]	Retro	9 mo	(1/29 pt)	3.4%	2/	
Cyteval 1999[10]	Prosp	6 mo	(5/20 pts)	25%	5/20	20%
Barr 20002[15]	Retro	18 mo	(1/38 pts)	3%	1/70	100%
Heini 2000[153]	Prosp	≥1 year	(2/17 pts)	12%	2/45	100%
Grados 2000[99]	Retro	48 mo	(13/25 pts)	52%	34/34	
Perez-Higueras 2002[80]	Prosp	5 years	(3/13 pts)	23%	4/27	50%
Zoarski 2002[85]	Prosp	15-18mo	(3/23 pts)	13%		
Uppin 20032[18]	Retro	24 mo	(22/177 pts)	12%	36	67%
Diamond 2003[114]	Prosp	7 mo	(3/55 pts)	5%		
Lin 2004[219]	Retro	12 mo	(14/38 pts)	37%	/96	50%
Legroux-Gerot 2004[168]	Prosp	35 mo	(7/16 pts)	44%	12/21	50%
Kim 2004[220]	Retro	3 years	?/106 pts		72/212	
Chen 2005[109]	Retro	12 mo	2/27 pts	7.4%	2/27	
Kobayashi 2005[98]	Prosp	15 mo	31/175	18%	36/250	58%
McKiernan 2005[113]		6 mo	3/46	7.3% ?		50%
Do AJNR 2005[221]	Prosp	6-32 mo	29/167	17%		62%
Syed AJN 2005[222]	Retro	12 mo	55/253 pts	22%	121/511	50%
Voormolen 2006[138]	Prosp	12 mo	(16/66 pts)	24%	26/102	54%
Prather 2006[87]	Prosp	12 mo	(10/50 pts)	25%	14/103	
Trout 2006[223]	Retro		(86/432 pts)	20%	186/	41%
Tanigawa 2006[224]		11.5	28/76 pts	37%	56/206	68
Lee 2006[225]	Retro	52 mo	38/244 pts	15.6%	/382	
PBK						
Theodorou 2002[129]	Retro	NR	(3/15 pts)	20%		
Lieberman 200[348]	Prosp	4 mo	(12/52 pts)	23%		
Phillips 2003[128]	Prosp	NR	(5/29 pts)	17%	5/61	60%
Fribourg 2004[226]	Retro	8 mo	(10/38 pts)	26%	17/47	76%
Kasperk 2005[115]	Prosp	6 mo	(5/40 pts)	12.5%		
Komp 2004[118]	Prosp	6 mo	(7/19 pts)	37%		
Rhyne 2004[94]	Retro	9 mo	(7/52 pts)	13.5%	/82	
Harrop 2004[227]	Retro	11 mo	(26/115 pts)	23%	34/225	65%
Gaitanis 2005[64]	Prosp	18 mo	(2/27 pts)	7.4%		
Majd 2005[103]	Retro	21 mo	30/254	12%	36/360	
Ledlie, Renfo 2006[101]	Retro	2 years	(7/77 pts)	9%	9/97	67%
Lavelle 2006[228]	Retro		13/94 pts	14%	16/109	56%
Garfin 2006[93]	Prosp	2 years	23/100 pts	23%		61%

fracture tended to have a higher number of vertebral levels treated. Survival time of kyphoplasty procedures that resulted in adjacent fractures was 112±145 versus 237±268 for distant VB fracture. However, the difference in survival time was not statistically significant.

Natural history of untreated disease: Determining whether the reported fracture rate after PVP or PBK is excessive presumes knowledge of the expected fracture rate in patients that have already sustained an OVCF. Lindsay et al (15) reported an incidence of 19.2% of new vertebral fractures within one year following one or more vertebral fractures in patients with osteoporosis. In women with one previous fracture the incidence was 11.5%, whereas this incidence was 24% in women with two or more fractures. Therefore, the presence of one or more vertebral fractures increased the risk of sustaining a new vertebral fracture five-fold during the following year. Ross et al (16) reported that a single fracture increases the risk for new vertebral fractures five-fold, while the presence of two or more fractures increases the risk 12-fold. A combination of low bone mass and the presence of two or more prevalent fractures increase the risk by 75-fold, relative to women with the highest bone mass and no prevalent fractures.(16) The severity of vertebral collapse (229) and the administration of glucocorticoids (230) have also been associated with the risk for new fracture. Silverman et al (21) reported that 58% of women with one or more fractures had fractures at adjacent vertebrae, supporting the high rate of adjacent fracture in the natural history of the disease. The temporal clustering of incident fractures has also been described. Furthermore, Kaplan et al (231) observed the clustering of incident fractures within eight months of diagnosis of a prevalent fracture. Therefore, it is possible that in the natural history of the disease, subsequent vertebral fractures tend to rapidly follow prevalent fractures even in the absence of cement augmentation.

Effect of deformity reduction on fracture risk: Balloon kyphoplasty may decrease the risk of new fractures, as it is indicated by some studies comparing it to either PVP or conservative treatment (**Table 12**). Kasperk et al (115) reported that at the six month follow-up, 12.5% (5/40) of patients who underwent PBK developed new fractures, as compared to 30% (6/20) of patients who were treated by conservative therapy. At the 12 month follow-up, the incidence of new fractures was 17.5% (7/40) for PBK and 50% (10/20) for the conservatively treated patients.(111) Regarding the incidence of the adjacent level fractures in that series, at six months was 6% in the PBK treated group versus 12% in the conservatively treated patients and at 12 months was 7.1% for PBK versus 9.7% for the conservatively treated patients.(111) Komp et al (118) reported new vertebral fractures in 37% of patients treated with PBK and 65% of patients treated conservatively. Only 40% of the new fractures after PBK were at adjacent VBs, while 100% of fractures in the conservatively treated group were at adjacent to the old fracture. However, in a prospective non randomized study that compares PVP with PBK, the authors reported that within the first four months one adjacent level fracture occurred in 29 levels treated with PVP, versus six adjacent fractures in 37 levels treated with PBK.(92) Furthermore, Kim et al (220) showed that the greater the degree of height restoration after PVP, the higher the risk of new fracture. Similarly, Lee et al (225) reported that the rate of developing new symptomatic OVCFs after PVP was inversely correlated with the degree of wedge deformation of treated VBs. In that study, the rate of developing new fracture was not related to the volume of cement injected nor the intradiscal leakage. The reason why the patients with lesser degree of initial wedge deformation are more prone to develop new symptomatic fracture remains unclear. A possible explanation may be that patients who retained more physiologic curvature at the time of PVP could turn more active and therefore exposed to more stressful environment.

Biomechanics of VB Cement Augmentation

In osteoporosis, the load needed to cause compressive failure of VBs (strength) and the ability of VBs to resist compressive deformation (stiffness) are diminished, as these mechanical characteristics are strongly correlated to bone density of trabecular bone.(232) Vertebral compression fractures result in a further reduction of both strength and stiffness relative to pre-fracture values.(233) The biomechanical goal of cement augmentation is to increase both the strength and stiffness of the fractured vertebra. However, it is unclear whether the aim should be to restore prefracture values. As osteoporotic vertebrae are at risk of fracture, restoring pre-fracture strength does not seem reasonable; trying to achieve healthy normal values is more desirable.(234)

Increasing the vertebral body strength may prevent further collapse. However, it is probably post-treatment stiffness that is responsible for pain relief. The adequate

Table 12. Comparison of the incidence of new fracture after PBK and conservative treatment.

	Kyphoplasty	Conservative	Follow up
Kasperk 2005* (115)	12.5% (5/40)	30% (6/20)	six months
Grafe 2005* (111)	17.5% (7/40)	50% (10/20)	12 months
Komp 2004 (118)	37% (7/19)	65% (11/17)	six months

*: Both authors refer to the same series of patients with different follow up periods.

restoration of stiffness creates a biomechanically stable environment and limits painful micromotion within the fractured vertebra. Consequently, painful micromotion may persist between fractured trabeculae if cement augmentation results in significantly decreased stiffness. However, it is often postulated that increasing stiffness to values significantly greater than that of the adjacent vertebrae may create a "stress riser" effect that could lead to mechanical failure of non-augmented levels.(235,236)

Effects of Augmentation on Treated Vertebrae

Cement volume: The strength and the stiffness of the augmented vertebra increases as a function of the volume of cement injected. As little as 2 mL of cement can restore vertebral strength to its prefracture values in all regions of the spine while volumes of 4 mL injected in the thoracic region and 6 mL injected in the lumbar region significantly increases strength.(237) However, as VBs vary considerably in size between regions and spines, restoration of strength may be better correlated to the percentage of the VB filled. Molloy et al (238) reported that restoration of strength required filling approximately 16% of the VB volume, which corresponds to fill-volumes of 2, 4 and 6 mL for the thoracic, thoracolumbar and lumbar regions, respectively. The correlation between cement volume and strength increase was reported to be weak in this study.

The increase of stiffness after vertebroplasty is also influenced by the volume of injected cement. Finite element modeling studies have suggested that only 14% of vertebral body volume, less than 3 cc of cement in the lumbar spine, is required to restore vertebral compressive stiffness in vertebroplasty; whereas 28% fill (7cc), commonly used in clinical practice, can increase stiffness to almost 50% above the intact value.(239) These estimates are not, however, confirmed in cadaveric studies. Molloy et al (238) reported that restoration of stiffness required approximately 30% of vertebral body volume: 4 mL in the thoracic region and 8 mL in the thoracolumbar region. In the lumbar region, stiffness was not restored even with a cement volume of 8 cc (the maximum volume used in the study). In a previous study, stiffness restoration was reported to require 4 mL of cement for the thoracic and thoracolumbar spine and 8 cc for the lumbar spine, possibly reflecting the importance of other factors other than cement volume.(237) In general, these studies show that larger volumes are needed for stiffness restoration than those required for strength restoration. Differences between various reports reflect the influence of other factors.

Bone mineral density: The increase in strength caused by augmentation is inversely related to bone mineral density (BMD).(240,241,242) This may be caused by the diminished strength of osteoporotic vertebral bodies, but also the greater degree of filling that can be achieved in osteoporotic vertebrae.(240) In nonosteoporotic, unfractured vertebrae, cement augmentation does not produce any significant changes in strength (240,242), but as little as 10% fill can result in large increases in compressive strength in osteoporotic lumbar vertebrae.(241)

There is debate in the literature concerning whether BMD affects the ability of cement augmentation to increase stiffness of vertebral bodies. Heini et al (240) reported that PMMA injection increased stiffness only in osteoporotic vertebrae. The augmentation effect was inversely related to BMD, but as the degree of filling was also inversely related to the BMD, this may reflect differences in the injected volume. Also, in this study vertebral bodies were injected without prior creation of a fracture. Belkoff et al reported that augmentation of fractured osteoporotic vertebrae did not restore their stiffness to prefracture values (234), although, in a previous study that used both osteoporotic and nonosteoporotic vertebrae, the same authors reported restoration of stiffness.(243) These findings suggest that restoration of prefracture stiffness by augmentation of fractured osteoporotic vertebrae may be unlikely.

Cement distribution: Most studies show that both bipedicular and unipedicular cement injections result in significant increase in strength; although the increase is reported to be greater with bipedicular injection.(233,241) In a finite element model, a posterolateral approach resulted in a higher stiffness than the bipedicular approach for all tested fill volumes; the difference increased with the volume of implanted cement.(239). Simulation of unipedicular injections resulted in equal or higher stiffness predictions compared with bipedicular or posterolateral cases. However, asymmetrical distribution of cement from a unipedicular approach resulted in a medial-lateral bending deformation toward the untreated side when uniform compressive load was applied and the authors advocated that bone cement is best introduced through a bipedicular approach to prevent risk of collapse on the nonaugmented side.(239) However, this risk has not been confirmed in cadaveric studies.(244) In a cadaveric study, lateral injection of 3.5 mL of cement restored stiffness of fractured vertebra to prefracture values, while central injections of the same volume resulted in significantly less stiffness.(244) When a larger amount of cement was used (7 mL), both central and lateral injections restored initial stiffness.(244)

Cement composition: Cements used for vertebral body augmentation are commonly altered by the addition of various opacifiers to increase visibility and by increasing the monomer to polymer ratio to decrease viscosity, increase working time and facilitate injection through a cannula.(26) These alterations change the cement's mechanical properties.

Belkoff et al compared Simplex P (Stryker-Howmedica-Osteonics, Rutherford, NJ, USA) mixed as directed by the manufacturer (10% BaSo4, and monomer to polymer powder ratio of 0.56 mL/g) with Simplex P modified as used in vertebroplasty (30% BaSo4, monomer to powder ratio of 0.71 mL/g).(245) They reported that fractured vertebrae augmented by vertebroplasty using the original Simplex P

resulted in significantly greater strength relative to their pre-fracture values, while those repaired with modified Simplex P resulted in significantly greater strength in the thoracic region and restoration of strength in the lumbar region. Postaugmentation stiffness also depends on cement composition. Fractured vertebral bodies injected with Simplex P were restored to pre-fracture stiffness levels, while those injected with Cranioplastic had significantly less stiffness.(243) Furthermore, the material properties of Cranioplastic are diminished when the cement is mixed as typically used in vertebroplasty.(246) In vertebroplasty studies, Cranioplastic resulted in lower vertebral body stiffness values than those in the intact state.(184,233,234) This does not appear to cause concern, as both cements are used clinically and there are no reported complications related to insufficient stiffness restoration.

Augmentation technique: In vertebroplasty, bone cement interdigitates into the cancellous bone, infiltrating the space between trabeculae; hence, at the periphery of cement mass, there are spikes of cement anchoring within the trabecular bone. In the balloon kyphoplasty model, a void is created within the VB and a layer of packed trabeculae displaced by balloon inflation surrounds this void. Three different and distinctive zones can theoretically be differentiated within the treated VB: an outer zone of intact bone, an intermediate zone of packed trabeculae and a central zone of cement.

Histological evaluation of retrieved vertebrae after PMMA augmentation revealed a few necrotic bone spicules associated with creeping substitution, suggesting either thermal lesions or devascularized trabeculae displaced by the procedure.(247,248) The cancellous bone surrounding the cement after kyphoplasty exhibits good density, supporting the concept that the displaced trabeculae by the expanding balloon is packed as autograft in the space around the cement.(247) Autograft packing at this site by displacement of trabeculae during balloon inflation can have a beneficial effect in maintaining stiffness and promoting remodeling. However, a decrease in stiffness can be expected in the period following the procedure owing to osteoclastic resorption of necrotic bone caused by the remodeling of the cancellous bone surrounding the cement.

Both vertebroplasty and kyphoplasty can significantly increase the strength of fractured vertebrae to above pre-fracture values. However, in one comparative study the increase after vertebroplasty was found to be significantly greater than after kyphoplasty.(184) In another cadaveric study it was shown that fractured VBs treated with kyphoplasty were initially taller that those treated with vertebroplasty. However, because of a progressive loss of height during repetitive cycling loading, the VBs treated with kyphoplasty were shorter than the ones treated with vertebroplasty. That leads to the conclusion that the cancellous bone around the cement zone is susceptible to further collapse, as been the weakest link in the chain of load transmission.(249) In vertebroplasty, cement inderdigitation throughout the VB may allow for better load transfer between the upper and lower endplated of the augmented vertebra. In clinical practice it is possible that even if subsequent collapse is not significant, microfractures at the non-augmented bone might account for relapse of pain after an initially successful augmentation procedure. Furthermore, there is evidence that loss of correction after PVP is greater for OVCF with clefts.(88) Pseudarthrotic cavity, being possibly less permeable to injected bone, prevents cement from interdigitating the cancellous bone leaving an area of nonaugmented trabeculae around the cement mass. A refracture of an augmented VB has been reported in a clinical series.(224) Therefore, to prevent further collapse of the treated vertebra, an attempt for the widest possible cement distribution within the treated vertebral body seems justified.

Effects of Augmentation on the Adjacent Vertebrae

Berlemann et al (235) using osteoporotic two-vertebra functional spinal units, showed a decrease in segment strength after cement augmentation in one vertebra. The ultimate failure strength of the functional units treated with injection of cement was on average 19% lower than in the match untreated controls and there was a trend towards lower failure loads with increased filling with cement. Overall stiffness of the augmented functional units was not significant different than the nonaugmented control group. However, these specimens were tested without first creating a compression fracture, and as mentioned previously, the stiffness of a fractured vertebra after cement injection is generally lower or at best restored to the intact (prefracture) value. Thus, the increased strains or loading of adjacent vertebrae cannot be attributed to the higher stiffness of the augmented vertebra. Furthermore, intervertebral disc, being the least stiff portion of the spinal segment should normally dissipate load stress in an even and physiologic way to prevent overloading of particular areas of adjacent vertebral bodies.

Finite models have predicted that rigid cement augmentation underneath the endplates acts as an upright pillar that reduces the inward bulge of the endplates of the augmented vertebra leading to increased pressure of the nucleus.(236,250) This leads to increased inward bulge of the endplate adjacent to the one augmented, supporting the hypothesis that rigid cement augmentation may facilitate the subsequent collapse of adjacent vertebrae. Nevertheless, these estimates were not confirmed in cadaveric models. End plate fracture decreases the pressure in nucleus pulposus by up to 25% (251), possibly reflecting the increased space available after the fracture. Ananthakrishnan et al (252) noted that although nucleus pressure was increased by cement augmentation, the resulting pressure was still below the level of the pre-fracture condition in all loading cases examined. As kyphoplasty has been shown to have better effects in reducing end plate fracture and mid vertebral body (253), it could be expected to have a better result in nucleus pressure

restoration. Still, although there was a small trend for better pressure restoration after balloon kyphoplasty versus vertebroplasty, the difference was not significant.(252) These data support that, although cement augmentation allows the disc to generate higher pressures compared to the postfracture state, the pressure still remains below that of the intact state, a finding that contradicts the hypothesis of increased end plate bulge of the adjacent vertebra. Furthermore, while stiffness of the augmented vertebra is influenced by cement volume, cement volume has not been shown to correlate with the rate of subsequent fractures in clinical studies.(219)

Load distribution between the trabecular centrum and the cortex is dependent on the properties of intervertebral discs.(254,255) Maintenance of nucleus hydrostatic pressure has an important role in spinal load transmission, as it allows the annulus to share the physiological load placed on spinal segments. A significant drop of nucleus pressure forces the annulus to bear axial loads (254), resulting in concentration of load anteriorly in flexion and posteriorly in extension.(256) Finite element models have demonstrated that a healthy disc, with a load-bearing nucleus, places more load on the trabecular centrum whereas a degenerated disc, with no load-bearing nucleus, places the majority of the load on the cortex.(254) A significant drop of disc pressure can cause the anterior vertebral body to be severely loaded when the spine is flexed.(256) Therefore, reduced nucleus pressure at the level of the fracture may result in redistribution of load to the periphery of adjacent vertebra, putting the anterior part of the vertebral body under increased loading when the spine is flexed, that might predispose to wedge fracture, especially in osteoporotic spines.

Another well-recognized risk factor for adjacent fracture is residual kyphotic deformity.(14,257,258) However, its contribution should be more important in the thoracic spine than in the lumbar spine, where osteoporotic factures tend to be biconcave and thus not significantly alter sagittal alignment. Residual kyphotic deformity after cement augmentation of a fractured vertebra may produce eccentric loading on adjacent levels, inducing additional flexion moments. Eccentric loading of a vertebra can increase peak stresses by up to 2.5-fold in vertebrae with reduced vertebral bone mass, possibly due to the development of high tensile and multiaxial stresses in the cortical shell and endplate.(259) Cadaveric studies have shown increased vertebral cortical strain at the adjacent vertebrae, especially in flexion.(260)

Mechanisms of pain relief

It has been hypothesized that pain relief is secondary to heat lesions of nerve endings produced by the exothermic reaction during polymerization of the PMMA cement.(261) Temperature measurements in human cadaveric vertebrae placed in a bath at 37°C ranged between 44-113°C in the anterior cortex, 49-112°C in the center, and 39-57°C in the spinal canal.(262) However, constant blood flow in live animals may have a cooling effect on bone cement, thus preventing temperature elevation capable of causing thermal damage. The mean peak temperature in the cement-bone interface recorded in the vertebral bodies of living goats was 44.6°C, while maximum temperature at the epidural space was 37°C.(263)

The neurotoxic effect of MMA monomer has also been hypothesized to contribute to pain relief, since the clinical improvement is not related to the amount of the injected bone cement volume.(39,240) However, in clinical studies of both PVP and PBK, Nakano et al reported that calcium phosphate (51) and calcium sulphate (Calcibon) (111) cements were as effective as PMMA in relieving pain. Calcium phosphate and calcium sulphate cements do not cure exothermally and is well known for their biocompatibility.(264)

An attractive explanation on pain relief can be attributed to the mechanical properties of VB augmentation. Kaemmerlen (38) suggested that cement stabilizes the microfractures within the bone and transmits part of the vertebral load, thus reducing painful micromotion and the load transmitted by the osseous structure. Another possible mechanism of pain relief is the restoration of indradiscal pressure after cement injection. Endplate fracture reduces pressure in the nucleus and increase the compressive loading of the annulus, particularly at its posterior portion.(265,251) Cement augmentation has been shown to partially restore intradiscal pressure and reduce peak stress in the posterior annulus in cadaveric studies. This might reduce shearing stresses in the annulus which can otherwise lead to delamination and pain.

Conclusions

OVCF, a common complication of osteoporosis, is frequently associated with disabling back pain and physical functional limitations that may lead to major disability and increased mortality.(14,27) Both PVP and PBK are shown to be efficient in controlling pain and improving daily activities with sustained results. Similar results are also obtained when treating osteolytic metastatic or benign tumors. These benefits, and the delight in whatever pain-free life is left in these patients, should also be considered a strong argument for a paradigm shift in the prompt management of metastatic osteolytic tumors of the spine.

Although some studies suggest that better results can be expected in more recent fractures, there is a substantial amount of evidence that quite satisfactory results can be expected even in chronic situations. This suggests that the length of time between fracture and surgery is not an absolute determining factor for pain reduction. Furthermore, when treating patients with “chronic pain,” the precise dating of the fractures is often difficult and its accuracy is probably limited. Patient selection should not be based on the age of OVCFs but largely on evidence of nonhealing on MR images or maybe bone scans and the degree of persistent pain (72,73,103), although the presence of abnormal mar-

row signal on MRI is not considered as an absolute prerequisition by some authors.(74)

It is apparent that postural reduction by hyperextension can improve the vertebral height of OVCF in hypermobile vertebrae (fresh fracture or pseudarthrosis). This situation can be exploited during vertebroplasty; however, it seems that kyphoplasty may achieve better restoration of VB height and kyphosis. It must be kept in mind that the radiographic methods for vertebral body height measurement are imprecise and do not measure the vertebral deformity as a whole. The data of VB height restoration in both techniques are muddled due to the fact that the results are reported with different methodologies (134), rendering comparison among and between the two techniques difficult, if not unrealistic.

Cement leakage is well tolerated in the majority of cases but can be the main source of major neurological complications and pulmonary embolism. The available reports support that PBK protects against cement extravasation during the procedure rendering this technique safer than PVP. The wide ranging incidence of cement extravasation during augmentation procedure and the more accurate detection by CT scan suggest that this complication is probably underestimated.

The risk of adjacent fractures after PVP and PBK is generally small in patients with primary osteoporosis, but significantly increases in patients with severe secondary osteoporosis. The risk seems to be increased in the first two or three months after both PVP and PBK.(138,218,220,223,226) After this period, it is reported to be similar to the natural history of the untreated disease (226), thus suggesting that cement augmentation enhances the clustering phenomenon that has been reported in the natural history of OVCFs. Two small prospective nonrandomized studies that compare kyphoplasty to conservative treatment indicate that kyphoplasty resulted in less subsequent VB fractures than conservative treatment. Whether this is attributed to better kyphosis correction remains unclear, as there are reports that greater degree of high restoration is correlated with higher risk of new fractures after vertebroplasty. The available studies do not allow definite conclusions because of a lack of good-quality prospective randomized trials addressing this issue. Furthermore, as half of the new fractures can be asymptomatic (138), studies that report only symptomatic vertebral fractures are inaccurate.

PBK has several potential benefits. The creation of a void within the vertebral body surrounded by packed trabeculae allows the insertion of more viscous cement with least possible pressure, thus minimizing the risk of cement leakage. The technique allows for better restoration of VB height and kyphotic deformity. This might result to better restoration of the sagittal alignment of the spine that will bring about a shift of the displaced centre of gravity backwards, therefore theoretically decreasing the risk factor for potential fractures. It is also conceivable that the corrected body posture may prevent or minimize the functional disability attributed to kyphotic deformity from osteoporosis.

A drawback of PBK is the high cost of the equipment, which has been estimated at 3500 Euros per level (266), whereas for vertebroplasty the cost is Can $300 to Can $600 (approximately 500 Euro) per level.(267) Another disadvantage of this procedure is the added cost and risk of general anesthesia, although it can be performed using local anesthesia. Because this procedure is lengthier and more painful than vertebroplasty for more than one level, this procedure is usually done under general anesthesia. A third problem is the higher radiation exposure during the procedure.(268,269) However, its biomechanical advantages and safety margins outweigh any dreadful complications from cement leakage such as serious neurological deficit, paraplegia and even death.

Long term outcomes of VB cement augmentation versus conservative medical antiosteoporotic treatment and the effectiveness between PBK and PVP remain to be determined in multicenter randomized controlled trials. With the existing data, it is almost impossible to directly compare the two methods because of discrepancies in patient selection criteria and in the clinical outcomes measures used by the different authors, nor to evaluate the cost effectiveness of PBK versus PVP. To determine the long-term outcomes of PBK and PBK versus conservative medical antiosteoporotic treatment, multicenter randomized controlled trials are needed. How unethical is it to deprive patients from potentially significant pain relief and suffering of vertebral augmentation? We all know that medicine is full of surprises. What was good medical treatment a few years ago may be invalid, if not dangerous today. An excellent example is the use of estrogen as the standard prophylactic antiresorptive osteoporotic medication for menopaused women. The carcinogenic effect of estrogen far outweighs the benefits.(270) Therefore while patients are enjoying the benefits of vertebral augmentation procedures, we believe that randomized controlled trials ought to be mandatory.

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